REMARKS

Claims 1-27 are pending in the application. These claims are subject to restriction requirement into Groups I to VII. Claims 1-3, 7-12, and 26 stand rejected. Claims 4-6 have been objected to. In view of the foregoing amendments and the following response, the Applicants believe the amended and new claims presented herein are allowable. Reconsideration and reexamination is respectfully requested.

DRAWINGS

In the Office Action, page 1, numbered paragraph 1, the Examiner indicates that the instant application has been filed with informal drawings. Formal drawings will be filed after the claims are allowed.

CERTIFIED COPIES

In the Office Action, page 1, numbered paragraph 2, the Examiner indicates that certified copies of the priority documents in the instant application have not been filed. These certified copies will be filed following allowance of the application.

CHANGE OF APPLICATION TITLE

The Applicants acknowledge the change of the patent application title by the Examiner.

RESTRICTION REQUIREMENT

The Applicants hereby affirm the *provisional* election of Group I without traverse made by the undersigned in a telephone conversation with the Examiner on October 7, 1997.

CLAIM REJECTIONS UNDER 35 USC §112, FIRST PARAGRAPH

Claim 1, with depending claims 2, 3 and 8-11, claim 7, claim 12 and claim 26 stand rejected under 35 USC §112, first paragraph for the reasons set forth in the Office Action.

The Applicants believe that the remarks below, the claims as amended, and the new claims obviate all §112 grounds of rejection raised by the Examiner.

In making the §112, first paragraph rejection, the Examiner posits, in numbered paragraph 26 of the Office Action, that the Applicant's disclosure is not enabling for any sequence: with 70% or more homology to the disclosed sequences, which has any 15 consecutive or non-consecutive nucleotides of the disclosed sequences, or which has any fragment of the disclosed sequences. She further alleges that the Applicant's disclosure is enabling only for claims limited to the sequences, and their complements, as disclosed in the specification.

The Applicants respectfully point out that the specification is replete with teachings enabling one skilled in the art to which the invention pertains, or with which it is most nearly connected, to make or use the invention commensurate with the scope of these claims.

For example, at page 14, line 18 through page 15, line 18 of the specification, the Applicants teach how to obtain the polynucleotide sequences of the claimed invention and their structure when they state, in pertinent part:

> Further preferred embodiments of the invention are polynucleotides that are at least 70% identical over their entire length to a polynucleotide encoding tRNA synthetase polypeptide having the amino acid sequence set out in Figure 2 [SEQ ID NO:2], and polynucleotides which are complementary to such polynucleotides. Alternatively, most highly preferred are polynucleotides that comprise a region that is at least 80% identical over their entire length to a polynucleotide encoding tRNA synthetase polypeptide of the *Staphylococcus aureus* DNA of the deposited strain and polynucleotides complementary thereto. In this regard, polynucleotides at least 90% identical over their entire length to the same are particularly preferred, and among these particularly preferred polynucleotides, those with at least 95% are especially preferred. Furthermore, those with at least 97% are highly preferred among those with at least 95%, and among these those with at least 98% and at least 99% are particularly highly preferred, with at least 99% being the more preferred.
>
> Preferred embodiments in this respect, moreover, are polynucleotides which encode polypeptides which retain substantially the same biological function or activity as the mature polypeptide encoded by the DNA of Figure 1 [SEQ ID NO:1].
>
> The invention further relates to polynucleotides that hybridize to the herein above-described sequences. In this regard, the invention especially relates to polynucleotides which hybridize under stringent conditions to the herein above-described polynucleotides. As herein used, the terms "stringent conditions" and "stringent hybridization conditions" mean hybridization will occur only if there is at least 95% and preferably at least 97% identity between the sequences. An example of stringent hybridization conditions is overnight incubation at 42°C in a solution comprising: 50% formamide, 5xSSC (150mM NaCl, 15mM trisodium citrate), 50 mM sodium phosphate (pH7.6), 5x Denhardt's solution, 10 % dextran sulfate, and 20 micrograms/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65°C. Hybridization and wash conditions are well known and exemplified in Sambrook, *et al.*, Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor, N.Y., (1989), particularly Chapter 11 therein, the disclosure of which is hereby incorporated in its entirety by reference.
>
> The invention also provides a polynucleotide consisting essentially of a polynucleotide sequence obtainable by screening an appropriate library containing the complete gene for a polynucleotide sequence set forth in SEQ ID NO:1 under stringent hybridization conditions with a probe having the sequence of said polynucleotide sequence set forth in SEQ ID NO:1 or a fragment thereof; and isolating said DNA sequence. Fragments useful for obtaining such a polynucleotide include, for example, probes and primers described elsewhere herein.

At page 11, last paragraph, the Examiner states that "[t]hese claims are drawn to encompass DNA fragments which encode all, a portion, or even a very small part of MetRS of *S. aureus*."

Moreover, the Examiner states, at page 12, first full paragraph of the Office Action, that "[s]ince detailed information regarding the structural and functional requirements of this protein is lacking, it is unpredictable as to which peptide fragments, if any, meet the limitations of the claims."

The Applicants do not agree with these views of the Examiner for the following reasons. Claim 1 of the instant application, as filed, recites "[a]n isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of: (a) a polynucleotide having at least a 70% identity to a polynucleotide encoding a polypeptide comprising amino acids 1 to 657 of SEQ ID NO:2; (b) a polynucleotide which is complementary to the polynucleotide of (a); and (c) a polynucleotide comprising at least 15 sequential bases of the polynucleotide of (a) or (b). The Applicants respectfully point out to the Examiner that the claim 1, as filed, is directed to polynucleotides that encode protein as well as polynucleotides that do not encode protein. The Applicant's specification provides numerous teachings of such coding and noncoding polynucleotides and their uses.

The noncoding polynucleotides are, for example, useful as primers and probes, including diagnostic probes, probes for staging infection progress, and research reagents. These noncoding polynucleotides include genes with an integrated phage, insertion sequence, or RNA edited sequence (refer to the specification at page 14, lines 6-7). The specification provides extensive teachings of noncoding polynucleotides as well as polynucleotides that encode the polypeptides

of the claimed invention. For example, at page 15, line 12 through page 16, line 6 of the specification, the Applicant's state, in pertinent part:

> The invention also provides a polynucleotide consisting essentially of a polynucleotide sequence obtainable by screening an appropriate library containing the complete gene for a polynucleotide sequence set forth in SEQ ID NO:1 under stringent hybridization conditions with a probe having the sequence of said polynucleotide sequence set forth in SEQ ID NO:1 or a fragment thereof; and isolating said DNA sequence. Fragments useful for obtaining such a polynucleotide include, for example, probes and primers described elsewhere herein.
>
> As discussed additionally herein regarding polynucleotide assays of the invention, for instance, polynucleotides of the invention as discussed above, may be used as a hybridization probe for RNA, cDNA and genomic DNA to isolate full-length cDNAs and genomic clones encoding tRNA synthetase and to isolate cDNA and genomic clones of other genes that have a high sequence similarity to the tRNA synthetase gene. Such probes generally will comprise at least 15 bases. Preferably, such probes will have at least 30 bases and may have at least 50 bases. Particularly preferred probes will have at least 30 bases and will have 50 bases or less.
>
> For example, the coding region of the tRNA synthetase gene may be isolated by screening using the known DNA sequence to synthesize an oligonucleotide probe. A labeled oligonucleotide having a sequence complementary to that of a gene of the invention is then used to screen a library of cDNA, genomic DNA or mRNA to determine which members of the library the probe hybridizes to.
>
> The polynucleotides and polypeptides of the invention may be employed as research reagents and materials for discovery of treatments of and diagnostics for disease, particularly human disease, as further discussed herein relating to polynucleotide assays, *inter alia*.
>
> The polynucleotides of the invention that are oligonucleotides, for example, those derived from the sequences of SEQ ID NOS:1 and 2, may be used in the processes herein as described, but preferably for PCR, to determine whether or not the polynucleotides identified herein in whole or in part are transcribed in infected tissue. It is recognized that such sequences will also have utility in diagnosis of the stage of infection and type of infection the pathogen has attained.

Moreover, at page 16, lines 7-23 of the specification, the Applicants teach further embodiments of polynucleotides that encode polypeptides, and state, in pertinent part:

> The polynucleotides may encode a polypeptide which is the mature protein plus additional amino or carboxyl-terminal amino acids, or amino acids interior to the mature polypeptide (when the mature form has more than one polypeptide chain, for instance). Such sequences may play a role in processing of a protein from precursor to a mature form, may allow protein transport, may lengthen or shorten protein half-life or may facilitate manipulation of a protein for assay or production, among other things. As generally is the

case *in vivo*, the additional amino acids may be processed away from the mature protein by cellular enzymes.

A precursor protein, having the mature form of the polypeptide fused to one or more prosequences may be an inactive form of the polypeptide. When prosequences are removed such inactive precursors generally are activated. Some or all of the prosequences may be removed before activation. Generally, such precursors are called proproteins.

In sum, a polynucleotide of the invention may encode a mature protein, a mature protein plus a leader sequence (which may be referred to as a preprotein), a precursor of a mature protein having one or more prosequences which are not the leader sequences of a preprotein, or a preproprotein, which is a precursor to a proprotein, having a leader sequence and one or more prosequences, which generally are removed during processing steps that produce active and mature forms of the polypeptide.

Also, at page 18, line 1 through page 19, line 23 of the specification, the Applicants teach diagnostic uses for and embodiments of polynucleotides that encode polypeptides as well as noncoding polynucleotides, and state, in pertinant part:

This invention is also related to the use of the tRNA synthetase polynucleotides of the invention for use as diagnostic reagents. Detection of tRNA synthetase in a eukaryote, particularly a mammal, and especially a human, will provide a diagnostic method for diagnosis of a disease. Eukaryotes (herein also "individual(s)"), particularly mammals, and especially humans, infected with an organism comprising the tRNA synthetase gene may be detected at the DNA level by a variety of techniques.

Nucleic acids for diagnosis may be obtained from an infected individual's cells and tissues, such as bone, blood, muscle, cartilage, and skin. Genomic DNA may be used directly for detection or may be amplified enzymatically by using PCR or other amplification technique prior to analysis. RNA or cDNA may also be used in the same ways. Using amplification, characterization of the strain of prokaryote present in a eukaryote, particularly a mammal, and especially a human, may be made by an analysis of the genotype of the prokaryote gene. Deletions and insertions can be detected by a change in size of the amplified product in comparison to the genotype of a reference sequence. Point mutations can be identified by hybridizing amplified DNA to labeled tRNA synthetase polynucleotide sequences. Perfectly matched sequences can be distinguished from mismatched duplexes by RNase digestion or by differences in melting temperatures. DNA sequence differences may also be detected by alterations in the electrophoretic mobility of the DNA fragments in gels, with or without denaturing agents, or by direct DNA sequencing. See, *e.g.*, Myers et al., *Science, 230:* 1242 (1985). Sequence changes at specific locations also may be revealed by nuclease protection assays, such as RNase and S1 protection or a chemical cleavage method. See, *e.g.*, Cotton et al., *Proc. Natl. Acad. Sci., USA, 85:* 4397-4401 (1985).

Cells carrying mutations or polymorphisms in the gene of the invention may also be detected at the DNA level by a variety of techniques, to allow for serotyping, for example. For example, RT-PCR can be used to detect mutations. It is particularly preferred to used

RT-PCR in conjunction with automated detection systems, such as, for example, GeneScan. RNA or cDNA may also be used for the same purpose, PCR or RT-PCR. As an example, PCR primers complementary to the nucleic acid encoding tRNA synthetase can be used to identify and analyze mutations. These primers may be used for amplifying tRNA synthetase DNA isolated from a sample derived from an individual. The invention also provides these primers with 1, 2, 3 or 4 nucleotides removed from the 5' and/or the 3' end. The primers may be used to amplify the gene isolated from an infected individual such that the gene may then be subject to various techniques for elucidation of the DNA sequence. In this way, mutations in the DNA sequence may be detected and used to diagnose infection and to serotype or classify the infectious agent.

The invention provides a process for diagnosing, disease, preferably bacterial infections, more preferably infections by *Staphylococcus aureus*, and most preferably disease, such as, infections of the upper respiratory tract (e.g., otitis media, bacterial tracheitis, acute epiglottitis, thyroiditis), lower respiratory (e.g., empyema, lung abscess), cardiac (e.g., infective endocarditis), gastrointestinal (e.g., secretory diarrhoea, splenic absces, retroperitoneal abscess), CNS (e.g., cerebral abscess), eye (e.g., blepharitis, conjunctivitis, keratitis, endophthalmitis, preseptal and orbital cellulitis, darcryocystitis), kidney and urinary tract (e.g., epididymitis, intrarenal and perinephric absces, toxic shock syndrome), skin (e.g., impetigo, folliculitis, cutaneous abscesses, cellulitis, wound infection, bacterial myositis) bone and joint (e.g., septic arthritis, osteomyelitis), comprising determining from a sample derived from an individual a increased level of expression of polynucleotide having the sequence of Figure 1 [SEQ ID NO: 1]. Increased or decreased expression of tRNA synthetase polynucleotide can be measured using any on of the methods well known in the art for the quantation of polynucleotides, such as, for example, amplification, PCR, RT-PCR, RNase protection, Northern blotting and other hybridization methods.

In addition, a diagnostic assay in accordance with the invention for detecting over-expression of tRNA synthetase protein compared to normal control tissue samples may be used to detect the presence of an infection, for example. Assay techniques that can be used to determine levels of a tRNA synthetase protein, in a sample derived from a host are well-known to those of skill in the art. Such assay methods include radioimmunoassays, competitive-binding assays, Western Blot analysis and ELISA assays.

The forgoing remarks clearly show that the specification teaches, among other things, polynucleotides that encode polypeptides as well as polynucleotides that do not encode polypeptides, such as, for example, polynucleotides that are fragments of coding sequence lacking translation signals, and uses thereof, such as for hybridization probing.

In view of the forgoing remarks, the Applicants respectfully submit that detailed information regarding the structural and functional requirements of the proteins of the invention

is provided for polynucleotide embodiments that encode polypeptides. However, for the polynucleotide embodiments that do not encode polypeptides no such detailed information is required to enable one skilled in the art to make and use them. The specification is replete with teachings that enable one skilled in the art to make and use the invention of claims 1-3, 7, 8-12 and 26, including the aforementioned coding and noncoding polynucleotide embodiments.

In view of the forgoing remarks, the new claims, and the claims as amended, the Applicants respectfully request that the Examiner withdraw her rejections, based on 35 USC §112, first paragraph of claims 1-3, 7, 8-12 and 26. The objection to claims 4-6 should also be removed.

CLAIM REJECTIONS UNDER 35 USC §112, FIRST PARAGRAPH

Claim 26 stands rejected under 35 USC §112, first paragraph for the reasons set forth in the Office Action. The Applicant's believe that the remarks below and claim 26 as amended obviates all §112 grounds of rejection raised by the Examiner.

At page 13, numbered paragraph 28 of the Office Action, the Examiner alleges that claim 26 is not properly enabled because the claim contains the phrase "obtainable" and the "obtainability" of a nucleic acid is not a reasonably determinable quality.

While the Applicants disagree that "obtainability" as used in the claim is not a reasonably determinable quality, to facilitate prosecution, the Applicants have amended claim 26 to no longer recite "obtainable." This amendment of claim 26 overcomes all grounds for its rejection based on 35 USC §112, first paragraph.

In view of the forgoing, the Applicants respectfully request that the Examiner withdraw her rejection of claim 26 based on 35 USC §112, first paragraph.

CLAIM REJECTIONS UNDER 35 USC §112, SECOND PARAGRAPH

Claim 26 stands rejected under 35 USC §112, second paragraph for allegedly being indefinite.

At page 14, numbered paragraph 29 of the Office Action, the Examiner asserts that the use of the phrase "consisting essentially of" renders claim 26 indefinite for the reasons set forth in the Office Action.

The Applicants have considered the Examiner's comments and have amended claim 26 to no longer recite "consisting essentially of" thus rendering moot the Examiner's rejection under 35 USC §112, second paragraph.

In view of the forgoing remarks and claim 26 as amended, the Applicant's respectfully request that the Examiner withdraw her rejection of claims 26 based on 35 USC §112, second paragraph.

CLAIM REJECTIONS UNDER 35 USC §102

Claims 1, 2, 7 and 8 stand rejected under 35 USC §102 as allegedly being anticipated by Bult et al. *Science 273(5278):* 1058-1073 (1996) (herein "Bult et al.") and Genbank submission U67567/L77117, made August 26, 1996 (herein "Genbank submission").

At page 15, numbered paragraph 30, the Examiner states that "Bult et al. teach a DNA molecule comprising at least 15 sequential bases of a polynucleotide encoding Seq. ID No.:2 (see attached sequence listing)."

The Applicants have amended claims 1 and 7 to no longer recite "a polynucleotide comprising at least 15 bases of the polynucleotide of (a) or (b)." Dependent claims 2 and 8, therefore, no longer posses the above quoted limitation.

In view of the forgoing remarks and claims 1 and 7 as amended, the Applicant's respectfully request that the Examiner withdraw her rejections of claims 1, 2, 7 and 8 based on 35 USC §102.

CLAIM REJECTIONS UNDER 35 USC §103(a)

Claim 1-3 and 7-12 stand rejected under 35 USC §103(a) as allegedly being unpatentable over Bult et al. and Georgiou AIChE J. 34(8): 1233-1248 (1988) (herein "Georgiou").

Bult et al. teach *Methanococcus jannaschii* DNA sequence that is merely identical across 15 bases to the Applicant's DNA that encodes the polypeptide of SEQ ID NO:2 (see Genbank submission sequence alignment provided by the Examiner). Moreover, the overall alignment provided by the Examiner shows 96 mismatches and 166 matches between the two sequences. The identity is not disclosed, but the Applicant's respectfully submit that the value must fall below the less stringent Best Local Similarity value of 63.4%.

Georgiou merely teach optimizing the production of recombinant proteins in microorganisms. Nowhere does Gorgiou teach or suggest any polynucleotide or polypeptide sequences.

Bult et al. neither teach nor suggest an isolated polynucleotide comprising a polynucleotide sequence having at least a 70% identity to a polynucleotide encoding a polypeptide comprising amino acids 1 to 657 of SEQ ID NO:2, as in the Applicant's claimed invention. Neither do Bult et al. teach an isolated polynucleotide comprising a polynucleotide having at least a 70% identity to a polynucleotide encoding the same mature polypeptide expressed by the tRNA synthetase gene contained in NCIMB Deposit No. 40771, as in the Applicant's claimed invention.

Georgiou fails to cure any of the deficiencies of Bult et al. Gorgiou further fails to teach or suggest any polynucleotide or polypeptide sequences of the Applicant's claimed invention. Georgiou merely provides general methods for practicing gene expression.

Using the teachings of Bult et al. and Georgiou, one skilled in the art would have no reasonable expectation of success of making or using the polynucleotide sequences of the Applicant's claimed invention. Moreover, Bult et al. teaches away from using its disclosed sequences to isolate a polynucleotide comprising a polynucleotide having at least a 70% identity to a polynucleotide encoding the same mature polypeptide expressed by the tRNA synthetase gene contained in NCIMB Deposit No. 40771, since the deposited clone is quite taxonomically divergent from the archaeon *Methanococcus jannaschii*, being from a different genus, as well as from a different Domain (see Bult et al. page 1058, paragraph 1). The Archaea, of which the *Methanococcus jannaschii* is a member, are in many respects more like Eukaryotes and may be specifically related to them (see Bult et al. page 1058, paragraph 1, lines 8-10). This reference therefore teaches one skilled in the art away from using *Methanococcus jannaschii* (an archaeon) to probe for a gene in a prokaryote, such as *Staphylococcus aureus.* Even if one skilled in the art does use *Methanococcus jannaschii* tRNA synthetase sequence disclosed in the Genbank submission to

probe for a polynucleotide of the Applicant's claimed invention, they would have no reasonable expectation of success in obtaining such polynucleotide. The teachings of Georgiou cure none of the aforementioned deficiencies of Bult et al.

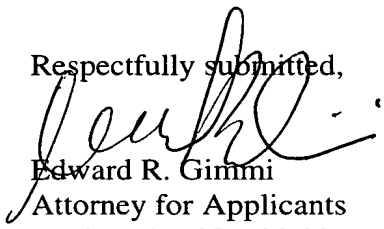
In view of the unobviousness of the polynucleotides in claims 1 and 7, the claims that depend therefrom are also unobvious as Georgiou merely teaches general methods of expression.

In view of the forgoing remarks, the Applicant's respectfully request that the Examiner withdraw her rejections of claims 1-3 and 7-12 based on 35 USC §103(a).

The Applicants reserve the right to prosecute claims to the non-elected invention in one or more patent applications.

The Applicants thank the Examiner for the Office Action and believe this response to be a full and complete response to such Office Action. Accordingly, favorable reexamination, reconsideration and allowance of the pending and new claims is earnestly solicited.

Respectfully submitted,



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